Good Clinical Practice in Research

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Purpose

To provide an overall understanding of the importance

good clinical practice in clinical research

Objectives

- **Historical Backdrop leading to GCP Guidelines**
  - Key Developments & Landmark Documents
- **GCP Guidelines**
  - Investigator's Responsibilities
- **Study Organization**
  - Keys to Successful Study Management

Food and Drug Law of 1906

- Upton Sinclair's investigation of the meat packing facilities in Chicago
  - Revealed unsanitary, filthy and unsafe conditions of meat packing process of the time and how the product was being transported to consumers
  - Sparked public and governmental outrage
- The first US law requiring food purity
- Prohibited the movement of misbranded or adulterated drugs, food, or beverages interstate
- The US government became the principal regulatory agent (later known as FDA) for this enterprise
- Purity of products required, safety or efficacy issues not addressed

Food, Drug & Cosmetic Act of 1938

- The Massengill Drug Company marketed elixir of sulfanilamide, an antibiotic
  - Released as a flu treatment
  - Killed 107 people, mostly children

- The elixir of sulfanilamide was found to be mixed with solvent ethylene glycol (antifreeze), which caused renal failure

Food, Drug & Cosmetic Act cont'd.

- First law requiring companies to establish drug safety prior to marketing
- Gave the FDA the authority to inspect drug manufacturing plants
- The Act was unenforceable and did not address efficacy

Nuremberg Code, 1947

- 1st document addressing ethical conduct in biomedical research following WW II atrocities
- Horrific experiments performed by physicians of Nazi Germany on victims of the concentration camps
- The code outlined the standards for conducting experiments on human subjects
- Landmark document on voluntary consent

Tuskegee Syphilis Study, 1932-1972

- Prospective drug trial evaluating the effects of untreated syphilis in poor black men
- Participants did not receive drug and unaware they were infected
- Treatment denied & withheld from study subjects during study; penicillin invented in 1942
- Most horrendous example of disregard for basic ethical principles in research
- $10 million paid out in settlements; formal apology in late 1990s by President Clinton

Thalidomide Tragedy

1962 Kefauver-Harris Amendments to the FDC Act

- Thalidomide Tragedy-the drug caused reportedly 10,000 cases worldwide of children born with birth defects and congenital disorders
- Used as sleep aid and to relieve morning sickness for pregnant women; considered safe and non-addicting
- It was sold OTC in Germany in 1957
- By 1960 it was sold throughout Europe, South America & Canada
- In 1960, Richardson-Merrell Pharmaceutical of Cincinnati submitted application to FDA to sell thalidomide under the brand name Kevadon

Kefauver-Harris Amendments cont'd.

- FDA received reports from overseas on the impact of the drug and issued a warning across the country
- 17 children were reportedly affected in America, however, no one really knows the true number
- Dr. Kelsey was praised for not giving in to the pressures to approve the drug
- Recently honored in September 2010 for her service and efforts with the FDA

Kefauver-Harris Amendments cont'd.

- Sponsors and manufactures required to
  1. Establish proof of efficacy in addition to purity and safety
  2. Submit results of two well-controlled double-blind trials as part of a New Drug Application (NDA) submission
  3. Obtain informed consent from research subjects prior to use of investigation drug; accurately and ethically advertise and recruit subjects
  4. Report adverse drug reactions

The Declaration of Helsinki

- An internationally recognized document, adopted in 1964; a comprehensive ethical approach to research
- A worldwide standard for medical personnel conducting human research trials
- Emphasized the proper safeguards and protections for human research, animals used in research
- Set the stage and scope of the bioresearch monitoring activities

U.S. Public Health Service

- In 1966, the US Public Health Service issued the first regulations on the Institutional Review Boards (IRBs) and the informed consent process involving human research subjects

The 1979 US Belmont Report

- Based on a comprehensive, federally commissioned review of human experimentation
  - explored ethical and human rights considerations & assist in resolving ethical issues
- Smithsonian Institution’s Belmont Conference Center
- Resulted in strenuous protections for human research subjects, greater respect for an individual’s autonomy, and attention to beneficence and justice when humans were involved in research
- It highlighted the informed consent and research subject selection processes
- Three key points . . .

The 1979 U.S. Belmont Report

- **Respect for subjects** – protection of individual autonomy and of those with diminished capacity
- **Beneficence** - do no harm, secure their well-being; maximize benefits & minimize risks
- **Justice** – share the benefits & burdens of research across society; fairness in distribution

“Common Rule” 32 CFR 219

- In 1991, the Common Rule became federal policy for the protection of human subjects
  - revised in 2001
  - Applies to DoD
  - Regulatory requirements of the Navy

Good Clinical Practice

What is it?

ICH GCP (E6), 1996

- International Conference of Harmonization (ICH) Tripartite Good Clinical Practice Guidelines (GCP) (E6)

- GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involved the participation of human subjects

Goal of GCP Guidelines

- Compliance with these standards provides public assurance that the rights, safety and well-being of trial subjects are protected
- Consistent with the principles that have their origin in the Declaration of Helsinki
- Clinical trial data are credible

FDA *vs.* GCP

- GCP guidelines are not codified in the U.S. federal regulation and are not legally binding as with the CFR
- However, the guidelines do not contradict the FDA regulations, but in fact represent the current thinking of the FDA and constitutes best practice in research
- GCP considered an FDA guidance document and applicable to all studies; think SOP

GPC Guidelines

- 13 Principles of GCP
- Institutional Review Board (IRB)
- Principal Investigator
- Sponsor
- Clinical trial protocol & protocol Amendments
- Investigator Brochure
- Essential Documents for the conduct of a clinical trial

Principles of GCP

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirements.
2. Before a trial is initiated, foreseeable risks and inconvenience should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

Principles of GCP

5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. Trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.

Principles of GCP

10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements.
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

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ACTION FIGURE!
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RESEARCHER
ENTREPRENEUR
WOW! COMES WITH DIFFERENT HATS FOR QUICK CHANGE of ROLES & RESPONSIBILITIES
BLINDERS to BLOCK OUT CONFLICT of INTEREST
IMPRESSIVE, DAZZLING WHITE LAB COAT!
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Investigator Responsibilities

- **Investigator's Qualifications and Agreements**
  - Qualified by education, training & experience
  - Compliance with regulatory requirements & GCP
  - Permit monitoring/inspection by appropriate authority
  - Maintain list of appropriately qualified persons & delegation of duties

- **Adequate Resources**
  - Demonstrate potential for recruitment
  - Sufficient time to properly conduct & complete trial
  - Adequate number of qualified staff, facilities to conduct trial properly & safely
  - Research team is adequately informed about protocol, IP, & trial related duties

Investigator Responsibilities cont'd.

- **Medical Care of Trial Subjects**
  - Qualified physician (or dentist, when appropriate), responsible for trial-related medical (dental) decisions.
  - During trial, adequate medical care is provided for adverse events and when medical care is needed.
  - Notify subject's primary physician about participation if subject agrees.
  - Make reasonable effort to ascertain reasons for subject premature withdrawal from the trial, while fully respecting the subject's rights to withdraw.

Investigator Responsibilities cont'd.

- Communication with IRB/IEC
  - Have written and dated IRB approved protocol, informed consent, recruitment procedures, *etc.*
  - Provide IRB with current copy of the Investigator's Brochure (IB), if applicable, and updates to the IB
  - Provide all documents subject to review

Investigator Responsibilities cont'd.

- Compliance with Protocol
  - Conduct study in compliance with the protocol
    - Some consider the protocol the "Bible" in research
  - Should not deviate or make changes to the protocol without submitting an amendment and documented IRB approval

Investigator Responsibilities cont'd.

- Informed Consent of Trial Subjects
  - Comply with applicable regulatory and ethical guidelines
  - Follow guidance in obtaining and performing informed consent process (specifics are outlined in the guidelines)

- Safety Reporting
  - Ensure serious adverse events are reported immediately to the IRB and sponsor, if applicable and in accordance with applicable regulatory guidelines

Investigator Responsibilities cont'd.

- Investigational Product/device(s)
- Randomization Procedures and Unblinding
- Records and Reports; Progress Reports
- Premature Termination or Trial Suspension

How do you manage these requirements?

Study Organization

- Is the key to successful management of study/trial

- Use:
  - The Regulatory/Administrative Binder
  - NMCP approved forms/templates
    - Provide uniformity, consistency and co
      especially in a transitional military env

Forms and Templates

- Approved Forms and Templates available:
  - Delegation of Duties Log
  - Training Log
  - Monitoring Log
  - Adverse Event Log
  - Prior and Concomitant Medications Log
  - Communications Log
  - Product accountability Log
  - Enrollment Log, coordinator checklist, progress note verbiage, *etc.*

Resources

- Guideline for good clinical practice E6(R1).
  - http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html
- NMCP Clinical Investigation Dept Webpage –
  - https://intranet.mar.med.navy.mil/CID/index.asp
- Collaborative Institutional Training Initiative (CITI)
  - https://www.citiprogram.org

“If everyone is moving forward together, then success takes care of itself.”

~ Henry Ford

Questions?

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